



Plasma adrenomedullin levels and nasopharyngeal carcinoma prognosis



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ABSTRACT

Background: Adrenomedullin has been identified as a tumor growth factor. However, few studies have reported its relationship with cancer survival. We evaluated the prognostic value of pretreatment plasma adrenomedullin levels in nasopharyngeal carcinoma (NPC).

Methods: Plasma adrenomedullin levels of 258 NPC patients and 100 healthy controls were determined using enzyme-linked immunosorbent assay. Adverse event was defined as tumor progression or death from any cause during 5-year follow-up. The relationships between plasma adrenomedullin levels and 5-year mortality, adverse event, tumor-free survival and overall survival were evaluated using multivariate analysis.

Results: Pretreatment plasma adrenomedullin levels were substantially higher in patients than in healthy subjects and were correlated highly with tumor classification, lymph node classification and tumor node metastasis stage positively. Adrenomedullin was identified as an independent predictor of 5-year mortality, adverse event, tumor-free survival and overall survival. Based on receiver operating characteristic curve analysis, pretreatment plasma adrenomedullin level had high predictive value for 5-year mortality and adverse event and had high diagnostic value for NPC.

Conclusions: Adrenomedullin may be a reliable biomarker for predicting the long-term prognosis of patients with NPC and also has potential diagnostic utility for NPC.

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1. Introduction

Nasopharyngeal carcinoma (NPC) is endemic in Southeast Asia, particularly in the southern provinces of China where 15–30 cases are diagnosed per 100,000 inhabitants/year [1]. Accurate prognostic stratification of patients at diagnosis is essential for selecting patients who are suitable for more aggressive treatment, especially when there is convincing evidence of the survival benefit of combined-modality treatment for patients with NPC [2]. Compelling evidence has emerged in recent years suggesting that the use of circulating prognostic biomarkers is a convenient way to achieve accurate prognostic prediction of NPC and has been considered to be worthy of exploration [3].

Adrenomedullin (ADM) is a 52-amino-acid peptide belonging to the calcitonin gene peptide superfamily based on its slight homology with calcitonin gene-related peptide and amylin [4]. ADM participates in a wide range of physiological and pathological events, including cell growth, vasorelaxation, angiogenesis and apoptosis [5,6]. There is accumulating evidence that ADM acts as a tumor growth factor [7–10]. ADM is therefore proposed as a therapeutic target in cancer [11,12]. Up to now, few studies have reported the relationship between ADM and cancer

prognosis. The aim of this study was to determine pretreatment plasma ADM levels in patients with NPC and furthermore verify the association between the pretreatment plasma ADM levels and NPC survivals.

2. Methods

2.1. Study population

This study evaluated 258 patients with pathologically proven NPC receiving complete radical radiotherapy with or without chemotherapy at Department of Otorhinolaryngology, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China between February 2006 and May 2008. The patients who had previous malignant diagnoses, concurrent malignancies, secondary tumors, severe infection and systemic autoimmune disease, had been excluded. This study also included 100 healthy controls. The study protocol was approved by the Chinese Ethics Committee of Human Resources at the First Affiliated Hospital, School of Medicine, Zhejiang University. Written informed consent was obtained from the study subjects.

2.2. Clinical assessment

For all patients, the following data sources were obtained: complete medical history, physical examination, full blood count, baseline serum biochemistry analysis including blood glucose, sodium, potassium, C-

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reactive protein, triglycerides, total cholesterol levels and so on, nasopharyngo-fiberscope inspection and nasopharyngeal tumor biopsy. All patients were classified according to the American Joint Committee on Cancer staging system.

2.3. Patient follow-up

After treatment, patients were followed up every 3 months for 3 years and thereafter every 6 months for 2 years. Overall survival (OS) was defined from the time of diagnosis to the time of death or until the last recorded follow-up visit if the patient was still alive at the end of the study. Adverse event was defined as tumor progression or death. Tumor-free survival (TFS) was defined from the time of diagnosis to the time of tumor progression, death, or last follow-up if the patient was still alive.

2.4. Immunoassay methods

Fasting blood samples were obtained from all patients before radical treatment and from the healthy volunteers at the physical examination day. After centrifugation (1500 × g for 20 min), plasma samples were stored at −70 °C. Plasma ADM concentrations were measured in duplicate using a commercial enzyme immunoassay kit (R&D Systems, Heidelberg, Germany) based on manufacturer's instructions. Intra-assay precision revealed a coefficient of variation of 4.9%, with an accuracy of 99%. The coefficient of variation of inter-assay precision was 5.6%, with an accuracy of 97%. Recovery was 94%. Claimed %CV was validated in the assay. The determination of ADM was performed every less than 6 months. The person carrying out the assays was completely blinded to the clinical information.

2.5. Statistical analysis

All statistical analyses were performed with SPSS 19.0 (SPSS Inc) and MedCalc 9.6.4.0. (MedCalc Software). All variables were expressed as the number or mean ± SD, unless otherwise stated. chi-Square tests and t tests were performed for intergroup comparisons. OS and TFS were estimated using the Kaplan–Meier method and the intergroup differences in survival time were tested using the log-rank test. A multivariate Cox's proportional hazard analysis was carried out to identify independent prognostic factors for OS and TFS with calculated hazard ratios (HR) and 95% confidence interval (CI). A binary logistic-regression analysis was performed to identify independent prognostic factors for 5-year mortality and adverse event with calculated odds ratio (OR) and 95% CI. All significant parameters in the univariate analysis were entered into a multivariate model. Receiver operating characteristic (ROC) curves were used to describe the predictive values with the estimated optimal cut-off point and the calculated area under curve (AUC). All $P < 0.05$ were considered as statistically significant with a 2-tailed test.

3. Results

3.1. Study population characteristics

This study included 258 NPC patients and 100 healthy individuals. There were not statistically significant intergroup differences in age and gender. These patients included 183 males and 75 females. Among them, 80 patients (31.0%) had an age of ≥50 years and 178 patients (69.0%) had an age of <50 years, 85 patients (33.0%) had tumor classification T_{3+4} and 173 patients (67.0%) had tumor classification T_{1+2} , 79 patients (30.6%) had lymph node classification N_{2+3} and 179 patients (69.4%) had lymph node classification N_{0+1} , 119 patients (46.1%) had tumor node metastasis stage III + IV and 139 patients (53.9%) had tumor node metastasis stage I + II, 126 patients (48.8%) had smoking history, 107 patients (41.5%) had alcohol consumption,

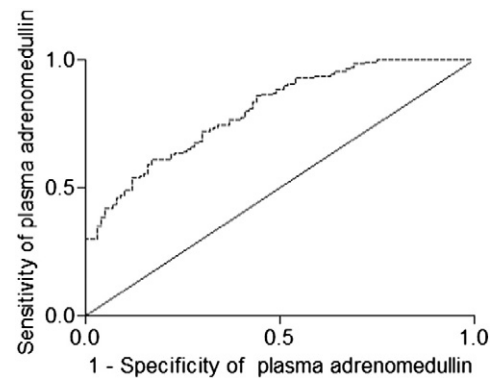


Fig. 1. The receiver operating characteristic curve analysis of plasma adrenomedullin levels for identifying nasopharyngeal carcinoma.

136 patients (52.7%) had chemotherapy and 15 patients (5.8%) had family history of NPC.

3.2. The change of plasma ADM levels

Plasma ADM levels were statistically significantly higher in the patients than in the healthy controls (62.0 ± 24.8 vs. 39.1 ± 12.2 pg/ml; $P < 0.001$). In addition, plasma ADM levels were bifurcated at mean value of 62.0 pg/ml. Value of >62.0 pg/ml indicated high ADM level and value of <62.0 pg/ml indicated low high ADM level. Among 258 NPC patients, 89 cases (34.5%) had high ADM level and 169 cases (65.5%) had low ADM level. Among 100 healthy controls, 3 subjects (3.0%) had high ADM level and 97 subjects (97.0%) had low ADM level. Using the χ^2 test, this difference was statistically significant ($P < 0.001$). A ROC curve identified that plasma ADM level >44.5 pg/ml diagnosed NPC with 72.1% sensitivity and 70.0% specificity (AUC, 0.804; 95% CI, 0.759–0.844) (Fig. 1). Table 1 showed that patients with high ADM level had higher grade of tumor classification, lymph node classification and tumor node metastasis stage compared with patients with low ADM level.

3.3. 5-Year mortality and adverse event prediction

During 5-year follow-up, 85 patients (33.0%) died and 111 patients (43.0%) suffered from adverse events. Table 2 showed that old age, higher grade of tumor classification, lymph node classification and tumor node metastasis stage and high ADM level were highly associated with 5-year mortality and adverse events positively. Table 3 showed their OR values and 95% CI. A multivariate analyses selected age (OR, 2.834; 95% CI, 1.421–5.650; $P = 0.003$), ADM level (OR, 12.716; 95%

Table 1

The factors associated with plasma adrenomedullin levels in patients with nasopharyngeal carcinoma.

| Characteristics | High adrenomedullin level | Low adrenomedullin level | P |
|---|---------------------------|--------------------------|--------|
| Number | 89 | 169 | |
| Age (≥50 y/<50 y) | 33/56 | 47/122 | NS |
| Gender (male/female) | 59/30 | 124/45 | NS |
| Tumor classification (T_{3+4}/T_{1+2}) | 46/43 | 39/130 | <0.001 |
| Lymph node classification (N_{2+3}/N_{0+1}) | 42/47 | 37/132 | <0.001 |
| Tumor node metastasis stage (III + IV/I + II) | 56/33 | 63/106 | <0.001 |
| Smoking history (yes/no) | 50/39 | 76/93 | NS |
| Alcohol consumption (yes/no) | 43/46 | 64/105 | NS |
| Chemotherapy (yes/no) | 53/36 | 83/86 | NS |
| Family History of nasopharyngeal carcinoma (yes/no) | 5/84 | 10/159 | NS |

Intergroup comparisons were performed using χ^2 tests.

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